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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,009	07/14/2006	Behrooz Sharifi	67789-080US0	6133

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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
08/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,009	SHARIFI ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,11-13 and 15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7,8,11-13 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 22, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 17, 2010 has been entered.

Claims 1, 3-5, 7-8, 11-13 and 15-19 are under consideration.

Priority

This application is a 371 of PCT/US04/22827 filed July 15, 2004. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/487,409, filed on July 15, 2003 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on July 22, 2010 that have been considered.

It is noted that the IDS submitted on July 22, 2010, list a number of International Search Reports for various International PCT applications. While the Search Report documents themselves have been considered, please note that the references cited in each search report have not been considered. The listing of references in a Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98.

37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration

by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper."

Therefore, as noted above, the references cited in each of the Search Reports listed in the IDS dated July 22, 2010 have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP §609.05(a).

The signed and initialed PTO Forms 1449 are mailed with this action.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 17, 2010 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

1. **Claims 15-19 stand rejected under 35 U.S.C. 101** because the claimed invention is directed to non-statutory subject matter.

Response to Arguments

Applicant continues to argue that the claimed endothelial cells do not encompass a human being. Rather, like a drug or dental implant, the claimed invention is only encompassed by a human being.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant is reminded that the substantive issue is that the scope of invention as claimed embraces a genetically modified human carrying in its genome or at least some of their cells a recombinant genetic material. Applicant's intended use of the monocytes transfected with a nucleic acid encoding PTN, thereby inducing differentiation into endothelial cells comprises promoting neovascularization to treat diseases such as ischemia by enhancing or promoting the activity of PTN (pg 8, ¶3). It is implicit that such patients are mainly human.

In contrast to Applicant's analogy to a drug or dental implant, the claimed endothelial cells will naturally become incorporated into human tissue [inseparable] and is structurally indistinguishable from the patient's tissue. A drug is quickly metabolized and excreted from the

body. A dental implant is both structurally distinguishable and separable from the [human] patient.

Consequently, when read in light of the specification the claimed host cells would include host cells in human patients that would be an integral and inseparable part of the human. Such cells that are part of a human are non-statutory subject matter since they embrace the human that carries them. It is USPTO policy not to allow claims to humans (1077 O.G. 24 April 1987). See MPEP §2105.

Claim Rejections - 35 USC § 102

2. **Claims 5, 8, 13, 15 and 17-19 are rejected under 35 U.S.C. 102(b)** as being anticipated by Scherman et al (U.S. Patent 5,945,400).

Scherman et al disclose endothelial cells (col. 10, line 57) transfected *in vitro* or *in vivo* (col. 10, lines 61-62) with a retrovirus (col. 1, line 39) encoding pleiotrophin (col. 9, line 3).

Scherman et al do not teach the endothelial cells are produced by the process of transdifferentiating RAW or THP-1 monocytic cells via a retrovirus expressing PTN. However, the recitation of a process limitation in the claims is not viewed as positively limiting the claimed endothelial cell product absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the endothelial cells were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

The instantly claimed endothelial cells are structurally indistinguishable from the endothelial cells of the prior art.

3. **Claims 5, 7-8, 13 and 15-19 are rejected under 35 U.S.C. 102(b)** as being anticipated by Colley et al (WO 99/53943; of record in IDS), as evidenced by Robbins et al (Trends Biotechnol. 16(1):35-40, 1998).

Colley et al disclose isolated endothelial cells treated with pleiotrophin (Example 1), wherein the pleiotrophin may be administered via a nucleic acid vector (pg 18, lines 5-7), i.e. a retrovirus (pg 19, line 32). Colley et al do not teach *ipsis verbis* that the retrovirus is a bicistronic retrovirus; however, Colley et al cite Robbins et al (1998) who taught the use of bicistronic retroviral expression vectors (pg 36), and thus those of ordinary skill in the art would immediately recognize Colley et al to disclose the use of bicistronic retroviral vectors, absent evidence to the contrary. Colley et al contemplate the target cells may also exist *in vivo* (pg 4, lines 6-8).

Colley et al do not teach the endothelial cells are produced by the process of transdifferentiating RAW or THP-1 monocytic cells via a retrovirus expressing PTN. However, the recitation of a process limitation in the claims is not viewed as positively limiting the claimed endothelial cell product absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the endothelial cells were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

The instantly claimed endothelial cells are structurally indistinguishable from the endothelial cells of the prior art.

Claim Rejections - 35 USC § 103

4. **Claims 1 and 11 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record).

Response to Arguments

The Examiner acknowledges and has considered the Natarajan Declaration filed under 37 CFR §1.132 on July 19, 2010.

The Natarajan Declaration is insufficient to overcome the rejection of recordas set forth in the last Office action because: while Applicant expresses statements regarding the underlying basis of Applicant's opinion and interpretation of the prior art, particularly Havemann et al, Applicant's opinion on the ultimate legal issue is not evidence, and Applicant has not provided factual support for the stated opinions.

Applicant argues that the Examiner has not analyzed the claimed subject matter as a whole. Rather, the Examiner has looked at whether the differences between the claimed invention and the prior art would have been obvious.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant's assertion that the examiner has not analyzed the claimed subject matter as a whole is factually incorrect. To clarify the record, the Examiner has performed the analysis of the instantly claimed invention as a whole, and has expressed the analysis in the prior Office Actions. The biologically inventive concept of the instant application is predicated upon the observation that monocytes differentiate into endothelial cells when stimulated by or exposed to pleiotrophin. However, the scientific concept that mononuclear cells [which includes monocytes] may differentiate into endothelial cells via stimulation by or exposure to PTN was previously taught by Havemann et al.

Applicant argues that the culture conditions of Havemann et al comprising glangliosides, phospholipids, glycolipids and growth factors are different conditions from using one growth factor, PTN, to induce differentiation per the instantly claimed invention.

Applicant's argument(s) has been fully considered, but is not persuasive.

As a first matter, the instantly claimed method uses open terminology "comprising", and thus other components may be present the claimed culture conditions in which the monocytic cell transdifferentiate into an endothelial cell. Thus, the instant claims do not exclude the use of glangliosides, phospholipids, and glycolipids per the Havemann et al disclosure.

As a second matter, Applicant appears to have mis-read the Havemann et al disclosure. Havemann et al disclose (b) culturing the cells in a cell culture medium comprising **one or more** [emphasis added] of glangliosides, phospholipids, glycolipids **and/or** growth factors for endothelial cells [0030]. Thus, glangliosides, phospholipids and glycolipids are **not required** to transdifferentiate mononuclear cells into endothelial cells.

Applicant argues that the actual examples do not include PTN in its culture media for differentiation. Thus, a general disclosure of culturing cells under differentiation conditions does not equate to a disclosure that PTN can be used to transdifferentiate monocytic cells into endothelial cells (Decl., ¶14, ¶17).

Applicant's argument(s) has been fully considered, but is not persuasive. A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). No undue experimentation is required. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072]. At the time of the instantly asserted invention (priority date of July, 2003), cell culture techniques were routinely practiced for several decades by the ordinary artisan, and it was routine in the art to apply PTN to cultured cells at various concentrations and for various amounts of time (Powers). Furthermore, the ordinary artisan need only provide PTN to the monocytes and observe the corresponding effect.

Applicant argues that Havemann et al do not teach the monocytic cells to be transduced with the retrovirus to transdifferentiate the cell into an endothelial cell (Decl., ¶15), and Souttou et al fail to make up for this deficiency.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that Havemann et al disclose the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene [0032, 0096], the effector gene being a growth factor [0047], e.g. angiogenesis growth factors. [0191]. Those of ordinary skill in the art had long-recognized that PTN is an angiogenic growth factor, thus the specific examples of VEGF and FGF [0191] are art-recognized species within the same genus of angiogenic growth factors that embraces PTN [0037]. Havemann et al cite Vile et al [0244] demonstrating that retroviral vectors were known in the prior art. (A copy of the Vile abstract is provided with the instant Office Action.) Given that Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072], Havemann et al is considered to provide a reasonable teaching and/or motivation for the ordinary artisan to transduce a monocytic cell with a retroviral expression vector encoding PTN to transdifferentiate the cell into an endothelial cell because the transdifferentiation of monocytes into endothelial cells naturally flows from the expression of PTN from the expression vector.

Applicant continues to argue that the Examiner has exercised impermissible hindsight in order to reject the claims, and is exercising cherry picking of particular disclosures to combine them in a way that does not reasonably flow from the combined teachings of the prior art.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the Examiner has taken into account only knowledge which was within the level

of ordinary skill at the time the claimed invention was made. Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072]. Havemann et al disclose the transfection of mononuclear cells with a nucleic acid construct for gene therapy, wherein the construct comprises an effector gene [0032, 0096], the effector gene being a growth factor [0047], e.g. angiogenesis growth factors. [0191]. Those of ordinary skill in the art had long-recognized that PTN is an angiogenic growth factor, thus the specific examples of VEGF and FGF [0191] are art-recognized species within the same genus of angiogenic growth factors that embraces PTN [0037]. Havemann et al cite Vile et al [0244] demonstrating that retroviral vectors were known in the prior art. Given that Havemann et al explicitly discloses that PTN is a growth factor that promotes the differentiation of mononuclear cells into endothelial cells [0066, 0072], Havemann et al is considered to provide a reasonable teaching and/or motivation for the ordinary artisan to transduce a monocytic cell with a retroviral expression vector encoding PTN to transdifferentiate the cell into an endothelial cell because the transdifferentiation of monocytes into endothelial cells naturally flows from the expression of PTN from the expression vector. Thus, it is unclear

Applicant is respectfully reminded that obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) In the instant case, Havemann et al disclose a working example using a pro-angiogenic growth factor, VEGF or ECGF (species within the same genus of angiogenic growth factors disclosed to have the property of promoting endothelial cell differentiation from mononuclear cells [monocytes]), to transdifferentiate mononuclear cells into endothelial cells (Example 3). Thus, absent evidence to the contrary, Havemann et al provide those of ordinary skill in the art with sufficient teaching, suggestion and a reasonable expectation of success for using PTN to transdifferentiate monocytes into endothelial cells.

5. **Claim 3 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J2002; *of record), as applied to Claims 1 and 11 above, and in further view of Kume et al (2000; *of record).

Response to Arguments

Applicant argues that Kume et al do not cure the defect of Havemann et al, Souttou et al and Powers et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al and Powers et al are discussed above and incorporated herein. Applicant does not contest the teachings of Kume et al as applied to the obviousness to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

6. **Claim 4 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 1, 3 and 11 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record).

Response to Arguments

Applicant argues that Pufe et al, Howett et al and Eslami et al do not cure the defect of Havemann et al, Souttou et al, Powers et al and Kume et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al and Kume et al are discussed above and incorporated herein. Applicant does not contest the teachings of Pufe et al, Howett et al and Eslami et al as applied to the obviousness to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

7. **Claim 12 stands rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 1, 3-4 and 11 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001).

Response to Arguments

Applicant argues that Kawamoto et al do not cure the defect of Havemann et al, Souttou et al, Powers et al, Kume et al, Pufe et al, Howett et al and Eslami et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al, Kume et al, Pufe et al, Howett et al and Eslami et al are discussed above and incorporated herein.

Applicant does not contest the teachings of Kawamoto et al as applied to the obviousness to substitute substitute the *in vitro* transdifferentiation step as taught by Havemann et al with an *in vivo* transdifferentiation step, with a reasonable expectation of success because the simple

substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, the motivation being that PTN has been repeatedly reported to induce the proliferation of endothelial cells and is an art-recognized angiogenic factor and Kawamoto et al successfully demonstrated the ability of monocytes to transdifferentiate into endothelial cells and incorporate at sites of neovascularization when implanted *in vivo*, thereby improving blood flow from an ischemic event.

8. **Claims 5, 13, 15 and 18 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (2002; *of record).

Response to Arguments

Applicant argues that Havemann et al, Souttou et al and Powers et al fail to render obvious the endothelial cell produced via transdifferentiation of a monocytic cell, for reasons discussed above.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al and Powers et al are discussed above and incorporated herein.

9. **Claims 7 and 16 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS) and Powers et al (J2002; *of record), as applied to Claims 5, 13, 15 and 18 above, and in further view of Kume et al (2000; *of record).

Response to Arguments

Applicant argues that Kume et al do not cure the defect of Havemann et al, Souttou et al and Powers et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al and Powers et al are discussed above and incorporated herein. Applicant does not contest the teachings of Kume et al as applied to the obviousness to substitute the retroviral expression vector by Havemann et al with a bicistronic retroviral expression vector as taught by Kume et al, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

10. **Claims 8 and 17 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record) and Kume et al (2000; *of record), as applied to Claims 5, 7, 13, 15-16 and 18 above, and in further view of Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record).

Response to Arguments

Applicant argues that Pufe et al, Howett et al and Eslami et al do not cure the defect of Havemann et al, Souttou et al, Powers et al and Kume et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al and Kume et al are discussed above and incorporated herein. Applicant does not contest the teachings of Pufe et al, Howett et al and Eslami et al as applied to the obviousness to substitute a first mononuclear/monocyte cell with a second monocyte cell, specifically THP-1, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

11. **Claim 19 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Havemann et al (*of record) in view of Souttou et al (2001; *of record in IDS), Powers et al (2002; *of record), Kume et al (2000; *of record), Pufe et al (2003; *of record in IDS), Howett et al (*of record) and Eslami et al (2001; *of record), as applied to Claims 5, 7-8, 13 and 15-18 above, and in further view of Kawamoto et al (Circulation 103:634-637, 2001).

Response to Arguments

Applicant argues that Kawamoto et al do not cure the defect of Havemann et al, Souttou et al, Powers et al, Kume et al, Pufe et al, Howett et al and Eslami et al.

Applicant's argument(s) has been fully considered, but is not persuasive. The Examiner's response to Applicant's argument(s) regarding Havemann et al, Souttou et al, Powers et al Kume et al, Pufe et al, Howett et al and Eslami et al are discussed above and incorporated herein. Applicant does not contest the teachings of Kawamoto et al as applied to the obviousness to substitute substitute the *in vitro* transdifferentiation step as taught by Havemann et al with an *in vivo* transdifferentiation step, with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, the motivation being that PTN has been repeatedly reported to induce the proliferation of endothelial cells and is an art-recognized angiogenic factor and Kawamoto et al successfully demonstrated the ability of monocytes to transdifferentiate into endothelial cells and incorporate at sites of neovascularization when implanted *in vivo*, thereby improving blood flow from an ischemic event.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Primary Examiner, Art Unit 1633